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BRIEF REPORT

Outcome and Disease Progression in NYHA Functional Class I and II Patients With Wild-Type Transthyretin Cardiomyopathy Treated With Tafamidis

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Wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) is a progressive cardiac disease caused by the deposition of misfolded transthyretin (TTR) in the myocardium, leading to increased wall thickness, diastolic dysfunction, and heart failure (HF). Tafamidis, a TTR stabilizer, reduced all-cause mortality and functional deterioration in the ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) trial, particularly in early-stage patients, and it received a class I recommendation in the 2021 European HF guidelines for patients with ATTRwt-CM and NYHA functional class I or II. Although real-world studies have confirmed the benefit of tafamidis, mortality and clinical progression remain relevant, underscoring the need for better tools to identify patients at higher risk of poor outcomes.[1]

What is the clinical question being addressed?
Among early-stage patients with ATTRwt-CM treated with tafamidis, what are the clinical outcomes and which clinical or biochemical markers can identify those at risk of disease progression and adverse events despite therapy?

What is the main finding?
Within 12 months of starting tafamidis, 9% of patients had events, and up to one-third exhibited markers of disease progression. Worsening in NYHA functional class, NAC/Mondor stage, NT-proBNP, eGFR, and ODI were associated with adverse prognosis.

Furthermore, no objective tools are currently validated to monitor disease progression under tafamidis treatment. Expert consensus recommends multidomain assessment—clinical, biochemical, and imaging based—but their application and prognostic value in tafamidis-treated cohorts are still poorly defined.[2] Recent data from untreated cohorts demonstrated that N-terminal pro-B-type natriuretic

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ABBREVIATIONS AND ACRONYMS

6MWTD = 6-minute walking test distance

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy

eGFR = estimated glomerular filtration rate

HF = heart failure

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

ODI = outpatient diuretic intensification

TTR = transthyretin

peptide (NT-proBNP) elevation, kidney function decline, and outpatient diuretic intensification (ODI) may serve as markers of disease progression.[3,4] Whether these criteria apply in tafamidis-treated patients remains unclear. This study investigated outcomes in early-stage ATTRwt-CM patients treated with tafamidis to evaluate the prognostic value of previously proposed progression markers and to identify baseline features associated with disease progression and poor prognosis despite treatment.

METHODS

This was a multicenter, longitudinal, observational study conducted in the ATTR-CM outpatient clinic of 19 Italian centers. The study was approved by the coordinating center's ethics committee (AOP3378), with local approvals obtained. It complied with the Declaration of Helsinki, and informed consent was obtained per institutional regulations. We included consecutive patients with a definitive diagnosis of ATTRwt-CM who initiated tafamidis between October 2021 (Italian approval) and December 31, 2022. Diagnosis was established by biopsy or by noninvasive criteria per European consensus, with TTR genetic testing performed in all patients to exclude hereditary forms. The exclusion criteria were NYHA functional class >II, unstable HF requiring diuretic adjustment at tafamidis initiation, enrollment in ATTR-CM trials, or compassionate-use tafamidis.

Clinical data were collected at baseline (defined as the day of tafamidis initiation) and at 12 months, including medical history, laboratory examinations, and echocardiography. The primary endpoint was a composite of all-cause death and HF hospitalization requiring intravenous diuretic administration. Continuous variables were expressed as median (Q1-Q3) and compared using Wilcoxon rank sum. Categorical variables were compared using chi-square test or Fisher's exact test. Two analyses were performed. The first was a time-to-event analysis from baseline using Cox regression after verifying proportional hazards. For patients without the endpoint, follow-up was censored at June 30, 2024. Multivariable models included variables significant in univariable analysis ($P < 0.05$) and those with clinical relevance: HF presentation (defined as the index heart failure event—requiring hospitalization and intravenous diuretic therapy—that led to the diagnosis of ATTRwt-CM and occurred within 12 months before enrollment), time from diagnosis to treatment, 6-minute walking test distance (6MWTD), NAC (National Amyloidosis Centre)/Mondor staging system, daily loop diuretic dose, left ventricular ejection fraction (LVEF), E/e′ ratio, and tricuspid annulus plane systolic excursion over systolic pulmonary artery pressure ratio. The second was a 12-month landmark analysis that excluded patients with prior events to avoid intervention-related bias. It assessed the prognostic value of progression markers: worsening NYHA functional class, NAC/Mondor stage, 6MWTD (decrease >35 m), estimated glomerular filtration rate (eGFR) (decrease >20%), NT-proBNP

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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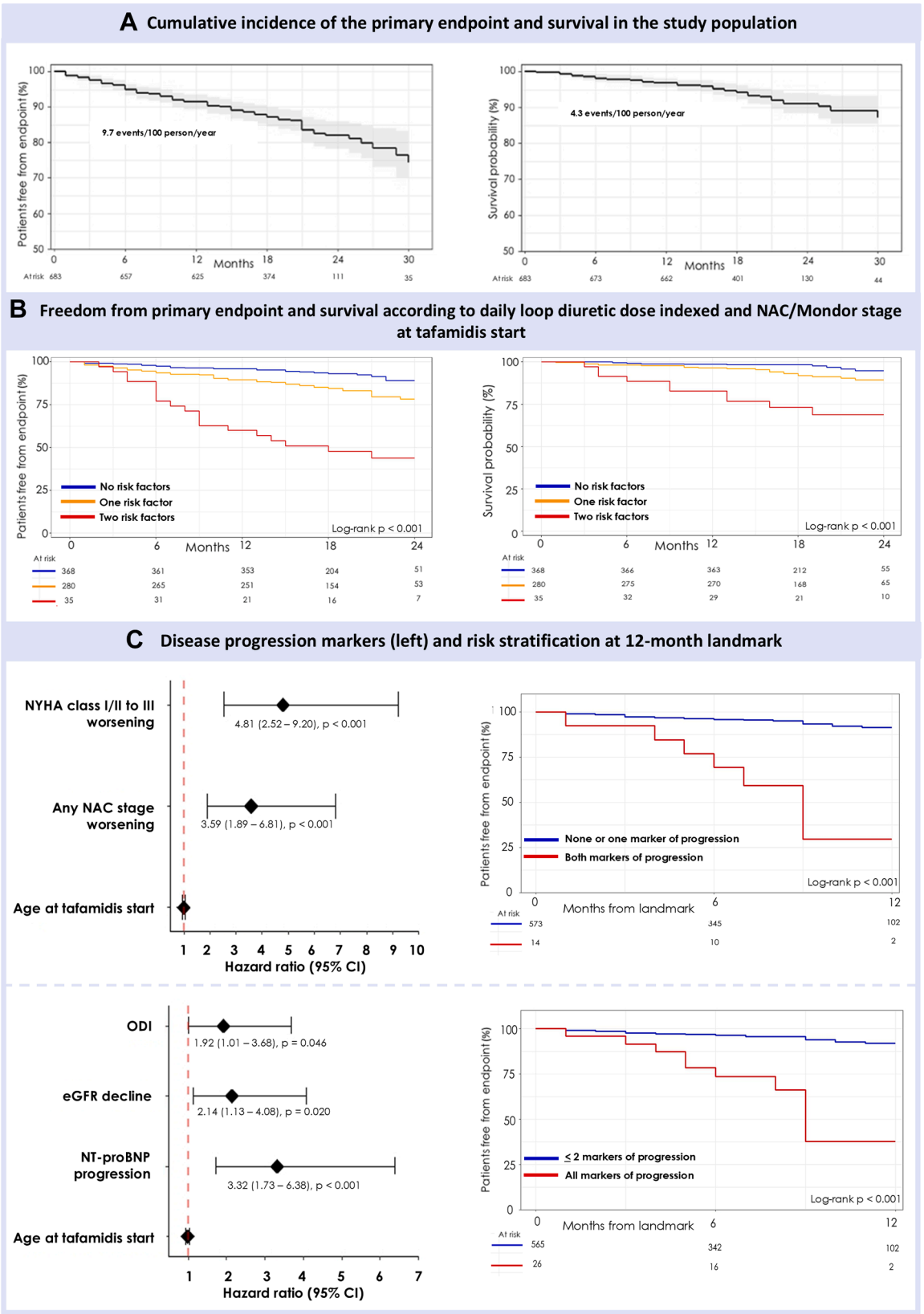
FIGURE 1 **Outcome and Disease Progression in Early Tafamidis-Treated ATTRwt-CM Patients**



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(absolute increase >700 ng/L and relative increase >30%), ODI (any initiation or dose increasing of loop diuretic drugs), left ventricular wall thickness (increase ≥2 mm), diastolic function (increase ≥2 in E/e′ ratio), and LVEF (decrease ≥5%). Cox regression was repeated from the 12-month time point.

Model collinearity was assessed with variance inflation factor and discrimination with Harrell's C-statistic. ORs and HRs, along with their 95% CIs, were calculated per 1-unit increase (for daily diuretic dose index per 0.5 mg/kg increments). Nonlinear associations for diuretic dose were explored using restricted cubic splines. Logistic regression identified baseline factors associated with progression. Survival was assessed using Kaplan-Meier and log-rank tests. Bonferroni correction was applied for multiple comparisons. Statistical analysis was performed using RStudio (v4.4.2; Posit).

RESULTS

The study population comprised 683 patients: 91% males, median age 78 years (Q1-Q3: 73-81 years), 31% >80 years. The median time from diagnosis to tafamidis start was 6 months (Q1-Q3: 2-15 months). One third (n =232, 34%) had prior HF presentation. Most patients were in NYHA functional class II (85%) and NAC/Mondor stage I (64%). Median values were 6MWTD: 375 m, NT-proBNP: 1,921 ng/L, and eGFR: 65 mL/min/1.73 m^2. Beta-blockers and loop diuretic agents were used in 59% and 72% of patients, respectively, with median daily furosemide-equivalent dose of 0.32 mg/kg.

Over a median follow-up period of 18 months (Q1-Q3: 15-22 months) after tafamidis start, the primary endpoint (all-cause death or HF hospitalization) occurred in 97 patients (15%), including 45 deaths (7%). The primary endpoint cumulative incidence was 9%, 13%, and 26% at 12, 18, and 30 months, respectively. All-cause mortality incidence was 3%, 6%, and 13% at the same timepoints (Figure 1A). Higher baseline daily loop diuretic dose (HR: 1.39 [95% CI: 1.21-1.59]; $P < 0.001$) and NAC/Mondor stage III (HR: 2.24 [95% CI: 1.08-4.65]; $P = 0.030$) were independently associated with the primary endpoint. The relationship between loop diuretic dose indexed and outcome was nonlinear ($P = 0.007$), with a significant change point in HR at 0.35 mg/kg of daily loop diuretic intake (HR: 0-0.35 mg/kg: 2.26 [95% CI: 1.47-3.49]; HR: 0.35-1.5 mg/kg: 2.65 [95% CI: 2.08-3.38]). Patients taking >0.35 mg/kg had a significantly worse outcome (log-rank $P < 0.001$), especially when combined with NAC/Mondor stage III (log-rank $P < 0.001$) (Figure 1B).

At 12 months, HF hospitalization occurred in 37 patients, who showed a markedly increased risk of subsequent death (HR: 9.59 [95% CI: 4.09-22.5]; $P < 0.001$). After excluding these patients and those who died (n = 58), 625 patients were eligible for landmark analysis. NT-proBNP progression, eGFR decline, and ODI occurred in 146 of 625 patients (23%), 117 of 591 patients (20%), and 210 of 625 patients (34%), respectively. Clinical deterioration included worsening NYHA functional class in 85 of 607 patients (14%), NAC/Mondor stage in 109 of 591 patients (18%), 6MWTD in 114 of 545 patients (21%), interventricular septum thickness in 86 of 535 patients (16%), LVEF in 113 of 550 patients (21%), and E: e' ratio in 151 of 397 patients (38%). Progression in NYHA functional class (particularly to class III), any NAC/Mondor stage, eGFR decline, NT-proBNP, and ODI were significantly associated with adverse outcomes (Figure 1C). Conversely, imaging-derived markers (interventricular septum, LVEF, and E/e′) and age showed no prognostic value.

After excluding collinearity between covariates (variance inflation factor <5), 2 multivariable risk models were developed: one including worsening to NYHA functional class III and NAC/Mondor stage and the other including ODI and worsening in eGFR and NT-proBNP. All variables were independently associated with the primary endpoint. Prognostic accuracy was comparable (Harrell's C: 0.71 and 0.72; $P = 0.2$). The contemporary presence of all markers of progression was associated with worse survival (Figure 1C). In logistic regression, HF presentation (OR: 1.63 [95% CI: 1.01-2.64]; $P = 0.046$), higher loop diuretic dose (OR: 1.95 [95% CI: 1.24-3.15]; $P = 0.005$),

FIGURE 1 Continued

(A) Cumulative incidence of the primary endpoint (left) and survival probability (right) in the overall study population. (B) Time to primary endpoint (left) and survival probability (right) stratified by the presence of baseline loop diuretic dose >0.35 mg/kg and NAC/Mondor stage III. (C) Independent risk factors for adverse outcomes at 12-month landmark analysis (left). Time to primary endpoint according to concurrent worsening of NYHA functional class to III and NAC/Mondor stage progression (top right), and according to concurrent NT-proBNP progression, eGFR decline, and outpatient diuretic intensification (bottom right). eGFR = estimated glomerular filtration rate; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ODI = outpatient diuretic intensification.

and systolic pulmonary artery pressure (OR: 1.03 [95% CI: 1.01-1.05]; $P = 0.010$) were independently associated with NYHA functional class I/II to III worsening or any NAC/Mondor worsening at 12-months after therapy start.

DISCUSSION

This study evaluated outcomes and disease progression in 683 tafamidis-treated ATTRwt-CM patients with NYHA functional class I-II symptoms. Over a median 18-month follow-up, 15% experienced death or HF hospitalization (9% within the first 12 months). Baseline NAC/Mondor stage III and loop diuretic dose >0.35 mg/kg were associated with worse outcomes. At 12 months, up to one-third showed signs of disease progression. Worsening in NYHA functional class, NAC/Mondor stage, NT-proBNP, eGFR, and ODI were associated with poor prognosis. Two risk models—one based on clinical progression and the other on biomarkers and ODI—showed comparable accuracy (C-statistic: 0.71 and 0.72) and may guide clinical monitoring and therapeutic decision-making in tafamidis-treated patients.

Until recently considered a rare, untreatable disease, ATTRwt-CM is now diagnosed earlier and more often in patients with milder phenotypes. Our cohort, mostly NYHA functional class I-II and NAC/Mondor stage I, showed 12-, 18-, and 30-month survival rates of 97%, 94%, and 87%, respectively—higher than those observed in earlier trials. Nonetheless, 9% experienced death or HF hospitalization within 12 months. Baseline NAC/Mondor stage III and high daily loop diuretic dose identified high-risk patients. At 12 months, worsening in NYHA functional class, NT-proBNP, eGFR, and ODI—but not imaging parameters—were associated with adverse outcomes. These findings suggest that disease progression under tafamidis can be assessed primarily through clinical and biochemical markers, as previously reported,[3-5] and they support earlier diagnosis and individualized treatment strategies in ATTRwt-CM.

STUDY LIMITATIONS. The results apply only to ATTRwt-CM patients in NYHA functional class I-II. Although some data were missing in the landmark analysis, the overall sample size remained robust. ODI was limited to loop diuretics. The 18-month follow-up may appear short but is likely appropriate for detecting early disease progression in early-stage patients, although longer-term trends and external validation will require further investigation.

CONCLUSIONS

Within 12 months of starting tafamidis, 9% of patients experienced HF hospitalization or death, and up to one-third exhibited markers of disease progression. Baseline NAC/Mondor stage III and a high daily loop diuretic dose were independently associated with adverse outcomes. Using a 12-month landmark analysis, we demonstrated that clinical and biochemical worsening over time was associated with subsequent events. Two progression-based models effectively identified high-risk patients and may help guide treatment decisions in clinical practice as well as serve as potential endpoints for future clinical trials.

DATA SHARING. The data underlying this paper cannot be shared publicly because of the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

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